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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BIGAUD ET AL.
APPLICATION NO: 10/581,068
FILED: NOVEMBER 9, 2006
FOR: BIOMARKERS FOR GRAFT REJECTION

Art Unit: 1634
Examiner: Kapushoc, Stephen Thomas

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

§ 1.144 Petition from Requirement for Restriction

Sir:

Applicants herewith petitions the Director for review and withdrawal of the restriction requirement issued by the Office September 19, 2008, traversed November 10, 2008, and made final in the Office Action issued February 13, 2009. No fees are believed due with this Petition.

The initial Restriction Requirement of September 19, 2008 identified six alleged groups of inventions. That restriction is reproduced below as follows:

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 1 and 2 in part as they require mRNA expression analysis, claims 6 and 13-15 as they depend from claim 1, and claims 9 and 10, drawn to methods for monitoring transplant rejection comprising analysis of mRNA expression.

Group 2, claim(s) 1 and 2 in part as they require protein expression analysis, claims 6 and 13-15 as they depend from claim 1, and claims 7 and 8, drawn to methods for monitoring transplant rejection comprising analysis of protein expression.

Group 3, claim(s) 3 in part as it requires mRNA expression analysis, drawn methods for monitoring transplant rejection comprising administration of an agent.

Group 4, claim(s) 3 in part as it requires protein expression analysis, drawn methods for monitoring transplant rejection comprising administration of an agent.

Group 5, claim(s) 4, drawn methods for affecting transplant rejection comprising administering a compound that alters gene activity.

Group 6, claim(s) 5, drawn methods for identifying an agent that affects transplantation rejection.

The Examiner's original argument for the restriction between these six groups is found on page 3 of the original Restriction Requirement, where it is stated:

4. The inventions listed as Groups 1-6 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:.

The inventions of Groups 1-6 lack unity of invention because even though the inventions of these groups require the technical feature of at least one gene that is recited in Table 1, 2, or 3 of the instant specification, this technical feature is not a special technical feature as it does not make a contribution over the prior art. For example, the gene of decorin (Table 2 on page 15 of the specification) was known in the prior art and is taught by GenBank Locus NM_133506 (2002). As such the common technical feature among the different groups is not a special technical feature in view of the teachings of the prior art.

The Examiner then discussed Markush practice under PCT Rule 13.2 (apparently due to claims 1-3 indicating that one may measure either mRNA or protein levels as a mode of measuring the

expression of the elected AIF-1 species in order to monitor transplant rejection). The remainder of the original Restriction Requirement details the requirement for a species election.

In the Reply to Restriction, filed by Applicants on November 10, 2008, Applicants elected Group I and species AIF-1. Applicants traversed both the species election and the restriction between groups I-IV. Regarding the restriction between groups I-IV, Applicants stated:

> Restriction between groups 1 and 2 is improper. In these two groups, the Examiner is restricting based on the mode of detection of the gene(s) of interest, said detection being via measuring either mRNA (group 1) or protein (group 2). Regardless of the mode of detection, the inventive concept between groups 1 and 2 is the same. The special technical feature that Applicant's invention contributes over the prior art is monitoring transplant rejection using the genes of Tables 1, 2 and 3. Applicant's have discovered that the genes of Tables 1, 2 and 3 are
>
> linked to the progression of transplant rejection, which feature is shared between groups 1 and 2, and which feature the Examiner has not identified in the art. The detecting modality one chooses to effect Applicant's inventions, e.g., detecting via a change in mRNA or protein, does not give rise to different inventions. The same may be said for groups 3 and 4. Accordingly, Applicants respectfully request withdrawal of the restriction between groups 1 and 2, and the restriction between groups 3 and 4.

In the Office Action, mailed February 13, 2009, the Examiner made final the requirement for species election and the restriction between groups 1-4, stating:

> 1. Applicant's election with traverse of the invention of Group 1 (i.e. claims drawn to methods for monitoring transplant rejection comprising analysis of mRNA) and the particular combination of genes consisting of AIF-1 (allograft inflammatory factor -1) in the reply filed on 11/10/2008 is acknowledged. The traversal is on the ground(s) that The special technical feature is the monitoring of rejection using the genes of Tables 1, 2, and 3 (where the particular gene AIF-1 is consonant with Applicant's election). This is not found persuasive because, as detailed in the art rejections in this Office Action, the increased expression of AIF-1 in rejection tissues was in fact known in the prior art. Further, the Examiner maintains that the claims as written drawn to the analysis of either mRNA or protein in the alternative lack unity of invention also because the different analytes (i.e. mRNA or protein) do not in fact share a common structure nor are they both part of the same class of chemical compounds.

Applicants respectfully submit that the restriction within claims 1-2 (groups I-II) and within claim 3 (groups III-IV) is improper. The Examiner bases this restriction, not on the subject matter that is claimed in independent claims 1-3 and their dependents (i.e., methods for monitoring transplant rejection by detecting the level of expression of the elected AIF-1), but rather on the particular mode used to detect the level of AIF-1, i.e., by measuring either the level of AIF-1 mRNA or the level of AIF-1 protein.

Applicants are not claiming mRNAs and proteins; Applicants' claims 1-3 (and their dependents) are all directed towards monitoring methods, which methods comprise a single invention. Whether one uses mRNA or protein as a means to measure the AIF-1 level is not germane to the inventive concept – monitoring transplant rejection. As there is a single monitoring invention among claims 1-2 and 3, unity of invention is satisfied under PCT Rule 13.1[1] for claims 1-2 and 3, and the restriction within these claims is improper.

The Examiner, however, believes that the monitoring claim should be divided into two separate inventions – a first monitoring method that analyzes mRNA levels of elected AIF-1 and a second monitoring method that analyzes protein levels of elected AIF-1. Thus, the Examiner argues that within claims 1-2 there are two inventions (separated by analysis of mRNA or protein levels) and within claim 3 there are two inventions (separated by analysis of mRNA or protein levels). As a result, the Examiner analyzes these claims under the "group of inventions" analysis found in PCT Rule 13.2[2]. According to MPEP 1850(III)(B), the Examiner applies Markush practice for unity of invention, and requires Applicants to identify a common property or activity and a common structure, apparently, for the mRNA and protein recited as capable of use in Applicants' monitoring methods. Assuming, *arguendo*, that the Examiner is correct in that there are a group of inventions recited in each monitoring claim (instead of a single invention as identified by Applicants), Applicants respectfully submit that the "invention" of monitoring transplant rejection by analyzing the level of mRNA of the elected AIF-1 species and the "invention" of monitoring transplant rejection by analyzing the level of protein of the elected AIF-1 species are so linked as to form a single general inventive concept.

According to the "PCT International Search and preliminary Examination Guidelines" (available at http://www.wipo.int/pct/en/texts/gdlines.htm), which describes unity of invention:

Rule 13.2 also governs the situation involving a single claim that defines alternatives

[1] Rule 13.1 The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

[2] Rule 13.2 Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

(chemical or non-chemical), the so-called "Markush practice." In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, is considered met when the alternatives are of a similar
nature.

(a) When the Markush grouping is for alternatives of chemical compounds, they are regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, that is, a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(b) In paragraph (a)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together.

(c) In paragraph (a)(B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

(d) The fact that the alternatives of a Markush grouping can be differently classified is not, taken alone, considered to be justification for a finding of a lack of unity of invention.

(e) When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention should be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity will be raised.

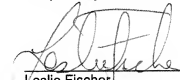
The above requirements of Markush practice under PCT Rule 13.2 are satisfied for using mRNA or protein to analyze the level of the elected species (AIF-1). First, the mRNA and protein have a common property or activity – both may be used to monitor transplant rejection. Second, both alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains as defined in (c), above. Specifically, because both mRNA and protein of AIF-1 are expected to be useful to measure the level of AIF-1, which level is used to correlate to transplant rejection "there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved."

Support for this interpretation of PCT Rule 13.2 may be found in 10.59, Example 39 on page 96 of "PCT International Search and preliminary Examination Guidelines" (available at http://www.wipo.int/pct/en/texts/gdlines.htm), which describes a situation in which claims are presented to DNA and the protein encoded thereby in a single application. In that Example, the PCT finds that because the claimed DNA molecule encodes protein X, protein X and the DNA encoding protein X share a corresponding technical feature. As a result, the claims shave unity of invention *a priori*. As noted above, Applicants are not claiming mRNAs or proteins, but the logic employed by the PCT for unity of invention in the biotechnological arts is clearly applicable here.

Additional support that the restriction within claims 1-3 is improper may be found in the Office Action, dated March 19, 2009 for U.S. Patent Application No. 11/574039. In this Office Action, Examiner Jennifer Dunston identified only three groups of inventions. Notably, Group I is directed to a method of early diagnosing or monitoring acute allograft rejection, comprising detecting a level of mRNA expression corresponding to **or** protein encoded by at least one gene in a body fluid. Examiner Dunston properly does not restrict between mRNA and protein detection, because these do not define separate inventions.

For at least the above reasons, Applicants submit that the restriction within claims 1-3 based on detecting mRNA versus protein is not proper. Please direct the Examiner of this application to withdraw that restriction such that these claims and their dependents may be examined in their entirety and on the merits.

Respectfully submitted,



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